

## **REMARKS/ARGUMENTS**

With this response claims 1-5, 16-20, 23 and 24 are pending. Claims 6-15 are withdrawn as drawn to a non-elected invention.

Applicants reserve the right to pursue, without prejudice, any subject matter including claim(s) as originally filed and/or otherwise set forth or described in this present application and/or in an earlier or other application(s) such as a priority application(s). No new matter is added.

## **CLAIM AMENDMENTS**

Claim 1 is amended for clarity by introducing the term “truncated thrombomodulin” with the second occurrence of “protein derivative.” In addition the term “EGF” is explicitly defined as “epidermal growth factor.” Support for this is found at page 9, lines 24-25 of the originally filed PCT application.

Claims 1 and 4 explicitly recite the leucine for methionine substitution is at position 40 of SEQ ID NO:3. Support for this is found at FIG. 1 and in SEQ ID NO:3 itself, where the <223> entry of the SEQ ID NO:3 (see page 3/6 of the Sequence Listing) states “Met-388-Leu substitution; position 40.”).

Claim 2 is amended by explicitly clarifying the position of the M residue as amino acid number 147 of SEQ ID NO:3. Support for this amendment is found at page 5, lines 19-20 of the PCT patent application (“In a preferred embodiment, a thrombomodulin derivative comprises a single non-natural amino acid at the C-terminal portion of the construct”) and in SEQ ID NO:3 (wherein the M amino acid residue is at position 147, the C-terminal portion, of the sequence).

Claim 3 is amended for clarity as suggested by the Office.

Withdrawn claims 6 and 8 are amended to be made dependent from claim 3 and to clarify that those claims relate to the amino acid sequence of SEQ ID NO:3 as recited in claim 3.

Claim 16 is amended for clarity by reciting a “truncated thrombomodulin protein derivative-polymer conjugate”.

Claim 17 is amended by spelling out the meaning of PEG as “polyethylene glycol.” Support for that amendment is found at page 2, lines 25-26 of the filed PCT application.

Claims 20 and 23 are amended for clarity by reciting “truncated thrombomodulin protein derivative.” Claim 20 is further amended by reciting a “catalytic active site” and that the non-natural amino acid is at the C-terminal portion of the derivative. Support for this amendment is found at page 5, lines 19-20.

Claim 24 is amended for clarity.

No new matter is added with this amendment, and entry of the claims presented herein is respectfully requested.

### **CLAIM OBJECTIONS (ITEM 3)**

The Office objects to claims 1 for a number of informality reasons. Applicants have adopted the Office’s suggestions by amending claim 1 for clarity. Applicants request the objection to claim 1 be reconsidered and withdrawn.

The Office suggests claim 2 be amended to recite “corresponding to the M amino acid residue of SEQ ID NO:X.” Applicants have accordingly adopted the Office’s suggestion.

Claim 3 is amended in accordance with the Office’s suggestion by explicitly noting that SEQ ID NO:3 is an amino acid sequence.

The Office suggests amending claim 16 for clarity by reciting a “thrombomodulin protein derivative-PEG conjugate.” Applicants have generally adopted the Office’s suggestion by reciting a “truncated thrombomodulin protein derivative-polymer conjugate”.

Claim 17 objected to the undefined use of the acronym “PEG.” Claim 17 is amended by providing the meaning of the term “PEG”.

Claim 20 is required to be amended to correct grammar by changing the term “catalytically” to “catalytic.” Applicants have accordingly amended claim 20.

Claims 20 and 21 are objected to for lack of consistency, and the Office requires amendment to read, “truncated thrombomodulin derivative.” As claim 21 is cancelled, Applicants believe this objection corresponds to claims 20 and 23 and have accordingly amended those claims for consistency.

Applicants believe every claim objection has been addressed and believes all the claims meet the Office’s formality requirements and requests the Office reconsider and withdraw all of the pending claim objections.

## **CLAIM REJECTIONS – 35 U.S.C. § 112**

### **ITEM 5**

The Office rejects claims 1-5 under 35 U.S.C. 112, first paragraph and alleges they contain “subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.” Applicants respectfully traverse this rejection in view of the amendments and remarks presented herein.

In support of this rejection, the Office states:

“Claims 1, 4 (and dependent claims 1-14 and 16) recite “leucine for methionine” and the instant specification discloses leucine is substituted for methionine at position 388 and not at other positions in [the] sequence set forth in SEQ ID NO:3. It is noted that SEQ ID NO:3 has 147 residues [and] thus does not have a position 388 as previously recited in the claims and is presently disclosed in the instant specification. Therefore, the specification lacks adequate written description.”

Applicants believe this rejection does not apply to claim 3, which is an independent claim that is directed to SEQ ID NO:3. Clarification is requested.

With respect to the “position 388” issue raised by the Office, Applicants refer the Office to FIG. 1 (bottom panel) of the instant specification, that provides a schematic structure of the truncated thrombomodulin protein, that runs from amino acid residue number 349 to amino acid residue 492 (e.g., 144 amino acids in length), with a Gly Gly Met at the carboxy terminus (e.g., total length of 147 (144+3) amino acids). In addition, the leucine substitution is explicitly illustrated in Fig. 1 as Leu388, with the 388 position being in reference to the full-length TM protein. Accordingly, position 388 of the TM protein is directly equivalent to position 40 of the amino acid sequence of SEQ ID NO:3 (e.g., position in truncated protein = 388 – 349 +1 = 40). In addition, inherently in SEQ ID NO:3, there is a substitution of Leucine for methionine at position 388 of the full-length TM, corresponding to position 40 of SEQ ID NO:3. Applicants draw the Office’s attention to SEQ ID NO:3, where at position 40 there is a leucine for methionine substitution, so that position 40 is, in fact, leucine. In the interest of clarity, however, Applicant explicitly recites in claims 1 and 4 that the leucine for methionine substitution has occurred at position 40 of SEQ ID NO:3. Accordingly, Applicants believe the claims do, in fact, satisfy the written description requirement and requests this rejection be reconsidered and withdrawn.

#### ITEM 6

The Office rejects claims 1-5 and 16-20 and 23-24 under 35 U.S.C. 112, first paragraph, alleging they contain “subject matter which was not described in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.” In particular, the Office apparently objects to the claims not setting forth what position in the structure of SEQ ID NO:3 the substitution will take place (citing claims 1 and 4). Applicants believe the amendment to claims 1 and 4 obviates this rejection, where the substitution is explicitly provided at residue 40 of SEQ ID NO:3.

With respect to the Office's allegation related to disclosure in the specification at position 388, and the fact that SEQ ID NO:3 only has 147 residues, the specification, including FIG. 1, clearly indicates that position 388 is, in fact, position 40 of SEQ ID NO:3. This is further supported in SEQ ID NO:3, where the <223> entry of the sequence (see page 3/6 of the Sequence Listing) states "Met-388-Leu substitution; position 40".

The Office apparently rejects claims that are drawn to a non-natural amino acid corresponding to the M amino acid residue (citing claim 2), without any reference to where in the structure this residue is. Solely to expedite prosecution, Applicants explicitly recite that the M amino acid residue is at position 147 of SEQ ID NO:3.

The Office similarly rejects claim 20. To further clarify the claimed invention, claim 20 is amended to recite the non-natural amino acid is at the C-terminal portion of SEQ ID NO:3. The Office notes that "claim 20 is directed to any non-natural amino acids." Applicants believe the specification provides adequate written description in support of claim 20, and specifically directs the Office's attention to page 5, lines 12-18:

In a preferred embodiment, a thrombomodulin derivative comprises a single non-natural amino acid or multiple non-natural amino acids. In an embodiment, a non-natural amino acid can include those as would be understood in the art. For example, non-natural amino acids can include: methionine analogues, alanine analogues, phenylalanine analogues, leucine analogues, proline analogues and isoleucine analogues. An example of methionine analogues includes: L-2-amino-4-azido-butanoic acid.

Accordingly, Applicants believe claims 2 and 20, specifically related to non-natural amino acids, satisfy the written description requirements and specifically request reconsideration and withdrawal of the rejection of these claims.

The Office notes claims 4, 16 and 23 are directed to a genus of polymers. Applicants believe the specification provides adequate written description to support the

claim to a genus of polymers. For example, page 5, line 26 – page 6, lines 21, provides various examples of natural and synthetic polymers.

The Office notes claim 24 is directed to a genus of mimetics. Solely in the interest of advancing prosecution, and to provide additional clarity to the claimed invention, Applicants delete the term mimetics and the term “other polymers.” Accordingly, Applicants believe claim 24 satisfies 35 U.S.C. 112, first paragraph.

Based on the amendments and arguments provided herein, Applicants believe the rejected claims each satisfy 35 U.S.C. 112, first paragraph, including written description. Accordingly, Applicants requests the rejection of claims 1-5, 16-20 and 23-24 under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

#### ITEM 7

Claims 1-5, 16-20 and 23-24 are rejected under 35 U.S.C. 112, second paragraph as allegedly failing to set forth the subject matter which applicants regard as their invention. The Office states:

“Claims 1-5 and 16-20 and 23-24 are indefinite for the recitation of ‘truncated thrombomodulin protein derivative comprising SEQ ID NO:3’ and a thrombomodulin protein derivative conjugated to a polymer comprising SEQ ID NO:3 as the structure of the protein and the structure of the conjugate cannot be the same.”

Applicants respectfully requests clarification of this rejection. For example, claims 1-3 relate to a truncated thrombomodulin protein derivative comprising SEQ ID NO:3. Claims 4-5, 16-20 and 23-24 in contrast, relate to a conjugate comprising SEQ ID NO:3 and a polymer. Accordingly, the conjugate structure of claims 4, 5, 16-20 and 23-24 and the protein structures of claims 1-3 are different, with the conjugate having a polymer conjugated to SEQ ID NO:3. Applicants request reconsideration and withdrawal of the 112 second paragraph rejection of claims 1-5, 16-20 and 23-24.

### **CLAIM REJECTIONS – 35 U.S.C. § 102 (ITEM 8)**

The Office rejects claims 1, 3-4, 16, 18 and 20 under 35 U.S.C. 102(b), citing U.S. Pat. No. 6,500,646 (Kuriyama et al.). Applicants respectfully traverse this rejection and notes that Kuriyama et al. does not teach or suggest the presently claimed invention SEQ ID NO:3.

The Office characterizes Claims 1, 3-4, 16, 18 and 20 as “a thrombomodulin protein derivative and a thrombomodulin protein derivative-polymer comprising SEQ ID NO:3 and a substitution of a leu for a met anywhere in the structure.” This is a fundamental mischaracterization of the claimed invention. In particular, the substitution of a leu for a met is at residue number 40 in SEQ ID NO:3. In addition, SEQ ID NO:3 has a GGM amino acid motif appended to the carboxy terminus. Neither the leu for met at position 40 nor the GGM motif are taught or suggested by Kuriyama. Accordingly, Kuriyama does not disclose SEQ ID NO:3 which contains leu for a met at residue number 40 or a GGM amino acid motif at the carboxy terminus. Applicants accordingly requests the 102(b) rejection of independent claims 1 and 16, and all rejected claims depending therefrom, be reconsidered and withdrawn.

**ITEM 9: Office's characterization in “Response to Arguments” section of the Office Action:**

For clarity, Applicants note there appears to be a fundamental mischaracterization of SEQ ID NO:3 by the Office. The Office appears to characterize the claimed invention as having a “substitution of leu to met” and that only one met residue is recited in SEQ ID NO:3. Applicants note that the claimed invention is a met to leu substitution (and not leu to met as characterized by the Office), and SEQ ID NO:3 already has this substitution in place at residue number 40 (corresponding to residue 388 of the TM sequence as noted in FIG. 1). Furthermore, as explained herein, there is direct support in the specification for the substitution at residue 40 of SEQ ID NO:3, as residue 40 of the truncated TM protein equals residue 388 of the TM protein sequence.

## REQUEST FOR REJOINDER

Applicants believe claim 3, directed to the amino acid of SEQ ID NO:3 is currently allowable, and specifically request claims depending therefrom, including withdrawn claims 6-12 be rejoined. In particular, claims 6 and 7 relate to a nucleic acid and are amended to be dependent from claim 3. Claims 8-12 are method claims that have been amended to depend from claim 3, and relate to a method of expressing the protein of claim 3 and specifically SEQ ID NO:3. Applicants specifically request that method claim 8, which contain all the limitations of the allowable product claim 3, and claims depending therefrom (claims 9-12) be rejoined in accordance with Office practice of rejoining method claims that contain all the limitations of the allowed product claim (see MPEP 821.04(b)).

## CONCLUSION

In view of the foregoing, Applicants believe the claims are in condition for allowance and respectfully requests the case be passed to allowance. It is believed that no fees or extensions of time are required with this submission. If this is not correct, please deduct any necessary fees from Deposit Account No. 071969. If any outstanding issues remain, the Office is encouraged to contact the undersigned by telephone.

Respectfully submitted,

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